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Effectiveness and safety of short *vs.* long duration of antibiotic therapy for acute bacterial sinusitis: a meta-analysis of randomized trials

Matthew E. Falagas,[1,2,3] Drosos E. Karageorgopoulos,[1] Alexandros P. Grammatikos[4] & Dimitrios K. Matthaiou[1]

[1]Alfa Institute of Biomedical Sciences (AIBS) and [2]Department of Medicine, Henry Dunant Hospital, Athens, Greece, [3]Department of Medicine, Tufts University School of Medicine, Boston, MA, USA and [4]Department of Medicine, 'G. Gennimatas' Hospital, Thessaloniki, Greece

Correspondence
Professor Matthew E. Falagas, MD, MSc, DSc, Alfa Institute of Biomedical Sciences (AIBS), 9 Neapoleos Street, 151 23, Marousi, Greece.
Tel: + 30 69 4611 0000
Fax: + 30 21 0683 9605
E-mail: m.falagas@aibs.gr

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Treatment guidelines generally support that a 10–14-day antibiotic regimen should be administered to uncomplicated acute bacterial sinusitis patients.
- However, the level of evidence for such a recommendation is rather weak.
- Treatment of such duration may have disadvantages compared with a shorter duration but equally effective regimen, including the promotion of bacterial drug resistance, poorest patient compliance, higher toxicity, and a greater overall economic burden.

WHAT THIS STUDY ADDS

- The findings of this meta-analysis suggest that short-course antibiotic treatment has similar effectiveness to longer-course treatment for patients with acute uncomplicated bacterial sinusitis, when treatment is warranted.
- However, we should underscore the importance of the clinician's own assessment, so that antimicrobial therapy should not inappropriately be curtailed in a patient not adequately responding to the regimen administered.

We sought to evaluate the effectiveness and safety of short-course antibiotic treatment for acute bacterial sinusitis (ABS) compared with longer duration treatment. We performed a meta-analysis of randomized controlled trials (RCTs), identified by searching PubMed and the Cochrane Central Register of Controlled Trials. We included RCTs that compared short-course (up to 7 days) *vs.* long-course therapy (≥2 days longer than short-course), with the same antimicrobial agent, in the same daily dosage, for patients with ABS. Twelve RCTs (10 double-blinded) involving adult patients with radiologically confirmed ABS were included. There was no difference in the comparison of short-course (3–7 days) with long-course treatment (6–10 days) regarding clinical success [12 RCTs, 4430 patients, fixed effect model (FEM), odds ratio (OR) 0.95, 95% confidence interval (CI) 0.81, 1.12]; microbiological efficacy; relapses; adverse events (10 RCTs, 4172 patients, random effects model, OR 0.88, 95% CI 0.71, 1.09); or withdrawals due to adverse events. In the sensitivity analysis comparing 5- *vs.* 10-day regimens, clinical success was similar, although adverse events were fewer with short-course treatment (5 RCTs, 2151 patients, FEM, OR 0.79, 95% CI 0.63, 0.98). Although antibiotics for acute sinusitis should be reserved for select patients with substantial probability of bacterial disease, accurate clinical diagnosis is often difficult to attain. Short-course antibiotic treatment had comparable effectiveness to a longer course of therapy for ABS. Shortened treatment, particularly for patients without severe disease and complicating factors, might lead to fewer adverse events, better patient compliance, lower rates of resistance development and fewer costs.

Introduction

Acute sinusitis (or rhinosinusitis, since concomitant inflammation of the nasal mucosa is the rule) represents one of the most common diagnoses in ambulatory care, and one of the most frequent causes for prescription of antibiotic treatment [1]. Confirmation of a bacterial aetiology is ordinarily not attained in routine clinical practice, since this requires antral puncture, or at least endoscopic sampling of the middle meatus [2]. Consequently, the choice of antibiotic therapy is empiric, in most cases, among agents potentially effective against the most frequently encountered upper respiratory tract pathogens, including *Streptococcus pneumoniae*, *Haemophilus influenzae* and, particularly in children, *Moraxella catarrhalis* [3].

Most pertinent treatment guidelines are in general agreement regarding the types of antibiotics recommended for the initial treatment of acute bacterial sinusitis (ABS) [4–7]. Regarding the appropriate duration of treatment, 10–14 days of antimicrobial therapy are most commonly recommended [4, 6]. This suggestion is mainly derived from the established microbiological efficacy of treatment for ≥10 days in ABS [4, 8], as well as from the lack of effectiveness associated with reducing the duration of antibiotic therapy for acute streptococcal tonsillopharyngitis [9]. However, data regarding the potential effectiveness of shorter duration regimens for ABS are rather limited [7]. Some experts believe that shortening the duration of antibiotic therapy for ABS is acceptable [5]. Moreover, such a strategy has not proven inferior compared with standard treatment in acute otitis media, which is caused by the same pathogens as acute sinusitis [10].

In this respect, we sought to evaluate the effectiveness and safety of treatment of ABS with the same antimicrobial agents in the same dosage, but for a different duration, by performing a meta-analysis of relevant randomized clinical trials (RCTs).

Methods

Data sources

The trials for this meta-analysis were retrieved from searches performed in PubMed, the Cochrane Central Register of Controlled Trials, and the bibliographies of evaluable studies. The search terms used were 'acute', 'sinusitis', 'rhinosinusitis', 'sinus infection', 'antibiotics', 'long', 'short', and 'duration'. Two reviewers independently performed the literature search, the evaluation of potentially eligible for inclusion studies and the extraction of data. Any discordance observed between the findings of the two reviewers was resolved in meetings of all authors.

Study selection criteria

Any of the identified trials was included in this meta-analysis if it had a randomized controlled design; involved patients of all ages with ABS, diagnosed on the basis of clinical criteria, with or without the use of complementary imaging, microbiological, or laboratory criteria; it compared treatment with the same antibiotic, in the same daily dosage, administered for a different duration of time (a short-course and a long-course); the short-course regimen had a duration of up to 7 days; there was a difference of ≥2 days between the short and long treatment course; it evaluated ≥30 patients in each of the relevant to this meta-analysis treatment arms; it reported data regarding clinical cure, microbiological efficacy, relapses, adverse events, or withdrawals due to adverse events. Trials including patients with mixed types of infection were included if they reported data specifically for the included patients with ABS, or, otherwise, if the patients with ABS constituted the great majority (>70%) of the study population. Conference abstracts or studies written in languages other than English, French, Spanish, Italian, German or Greek were excluded.

Quality assessment

Evaluation of the methodological quality of each of the RCTs included in this meta-analysis was performed by the Jadad criteria, which examine the existence of randomization procedures, blinded design, and information on study withdrawals, and evaluate the appropriateness of randomization and blinding, if present. One point is awarded for the presence of each of the former three criteria, whereas the latter two criteria are awarded the values of −1 (inappropriate), 0 (no specific data) and +1 (appropriate). Thus, the maximum score that can be attributed to a study is 5 points; a score >2 points denotes an RCT of adequately good quality, according to this scoring system [11, 12].

Data extraction

The data extracted from each included RCT regarded the type of study design, characteristics of the included population, the compared regimens, any concomitantly administered therapy, size of the intention-to treat (ITT) population, size of the per protocol (PP) population, timing of the test-of-cure visit, clinical and microbiological treatment outcomes, time to resolution of symptoms, as well as data on relapses, adverse events, and withdrawals due to adverse events.

Definitions

Acute bacterial sinusitis was defined by the presence of a constellation of characteristic clinical manifestations, including, among others, nasal congestion or obstruction, purulent rhinorrhoea, post nasal drip, facial pain or toothache, tenderness over the affected area, cough, fever, and halitosis, of <30 days duration [4]. The per protocol or, otherwise, evaluable population included patients that met the eligibility criteria for evaluation for a specific outcome, that were employed in each included trial.

The primary effectiveness outcome of this meta-analysis was clinical success of the PP population, which was defined as cure (complete resolution) or improvement of symptoms and signs of ABS, assessed at the time of the test-of-cure visit (otherwise described as the time of determination of the primary effectiveness outcome) of each included RCT. If data for the combined outcome of cure or improvement were not reported, data for cure alone were included. The secondary effectiveness outcomes included microbiological efficacy, defined as the eradication of pre-treatment isolated pathogens in post-treatment cultures or as presumed eradication, on the basis of the clinical outcome, if such cultures were not performed; and relapses, defined as the reappearance of signs and symptoms in patients who had been assessed as clinically cured or improved at the test-of-cure evaluation.

The primary safety outcome was adverse events, which included any adverse event observed until the end of the follow-up period in each included RCT. If, instead of any adverse event, only data regarding adverse events considered as drug-related were reported, we included the latter in the analysis. The secondary effectiveness outcome was withdrawals due to adverse events, which included patients who discontinued attendance to study protocols, due to any adverse event.

A sensitivity analysis was limited to trials that compared 5- *vs.* 10-day antibiotic treatment regimens. A subset analysis involved the comparison of short *vs.* long duration treatment with β-lactam agents alone.

Statistical analysis

All statistical analyses were performed using the statistical software 'RevMan Analyses v1.0 for Windows' (The Cochrane Collaboration, Copenhagen, Denmark). The presence of statistical heterogeneity between trials was assessed by the χ^2 test and the I^2 tests; a *P*-value of the χ^2-test of <0.10 was considered to denote the presence of statistically significant between-trials heterogeneity [13]. Publication bias, regarding trials of small sample size, was assessed by the funnel plot method [14]. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by both the Mantel–Haenszel fixed-effect model (FEM) [15], and the DerSimonian–Laird random-effects model (REM) [16]. For all analyses performed, if no significant between-trials heterogeneity was noted, results obtained with the FEM analysis are presented; otherwise, results of the REM analysis are presented.

Results

Study selection process

Figure 1 presents a flow diagram depicting the detailed process of screening and selecting articles to be included in the meta-analysis, which were retrieved from PubMed and the Cochrane Central Register of Controlled Trials. We identified 283 and 313 potentially relevant RCTs, respectively. We finally selected 12 RCTs [17–28] that fulfilled the criteria for inclusion in this meta-analysis.

Study characteristics

Table 1 presents the characteristics (type of patient population, drugs administered, concomitant therapy and timing of the test-of-cure visit) of each of the RCTs included in this meta-analysis. Regarding the methodological design of the 12 included RCTs, 10 were double-blinded [17–22, 24, 26–28]. Moreover, all but two of the included RCTs were assigned a Jadad score of at least 4 [17–20, 23–28]. Regarding study population, all of the included RCTs involved adult patients with uncomplicated ABS. Seven of the overall 12 RCTs referred particularly to patients with maxillary sinusitis [19, 20, 23–27]. The diagnosis of ABS was radiologically confirmed in all of the included RCTs. Furthermore, the required duration of symptoms of ABS prior to inclusion was >7–10 days in five RCTs [17, 20, 23, 24, 26]. Nine RCTs allowed the use of specific concomitant symptom relief medications [18, 19, 21, 23–28], which in two cases included the use of oral corticosteroids [18, 28].

Patients in the short-course treatment arms received therapy for 5 days in eight of the included RCTs [17–19, 21–23, 26, 27], for 3 days in two RCTs [20, 25], for 4 days in one RCT [28] and for 7 days in the remaining one RCT [24]. Patients in the long-course treatment arms received therapy for 10 days in 10 of the included RCTs [18, 19, 21–28] and for 6 days [20] and 7 days [17] in one RCT, respectively. In seven out of 12 RCTs [18, 19, 21–23, 26, 27] the duration of administered regimens was 5 and 10 days for the short-course and the long-course regimens, respectively. The antibiotics used were β-lactams in six out of 12 RCTs [18, 19, 24, 26–28], along with fluoroquinolones [17, 23], telithromycin [21, 22], azithromycin [20] and trimethoprim/sulfamethoxazole [25] in two, two, one and one RCTs, respectively. The timing of the test-of-cure visit in each included trial varied (minimum study day 10, maximum study day 22–36).

Outcomes

Table 2 presents the extracted data regarding the primary and secondary outcomes of this meta-analysis.

Clinical success Data on the primary effectiveness outcome of clinical success were provided in all 12 RCTs included in this meta-analysis [17–28]. No difference was found regarding clinical success between the short-course and the long-course regimens for the treatment of ABS (4430 patients, FEM, OR 0.95, 95% CI 0.81, 1.12; Figure 2).

In the sensitivity analysis comparing antimicrobial treatment of duration of 5 *vs.* 10 days [18, 19, 21–23, 26, 27], there was no difference in clinical success between the short-course and long-course regimens (seven RCTs, 2715 patients, FEM, OR 0.98, 95% CI 0.79, 1.22).

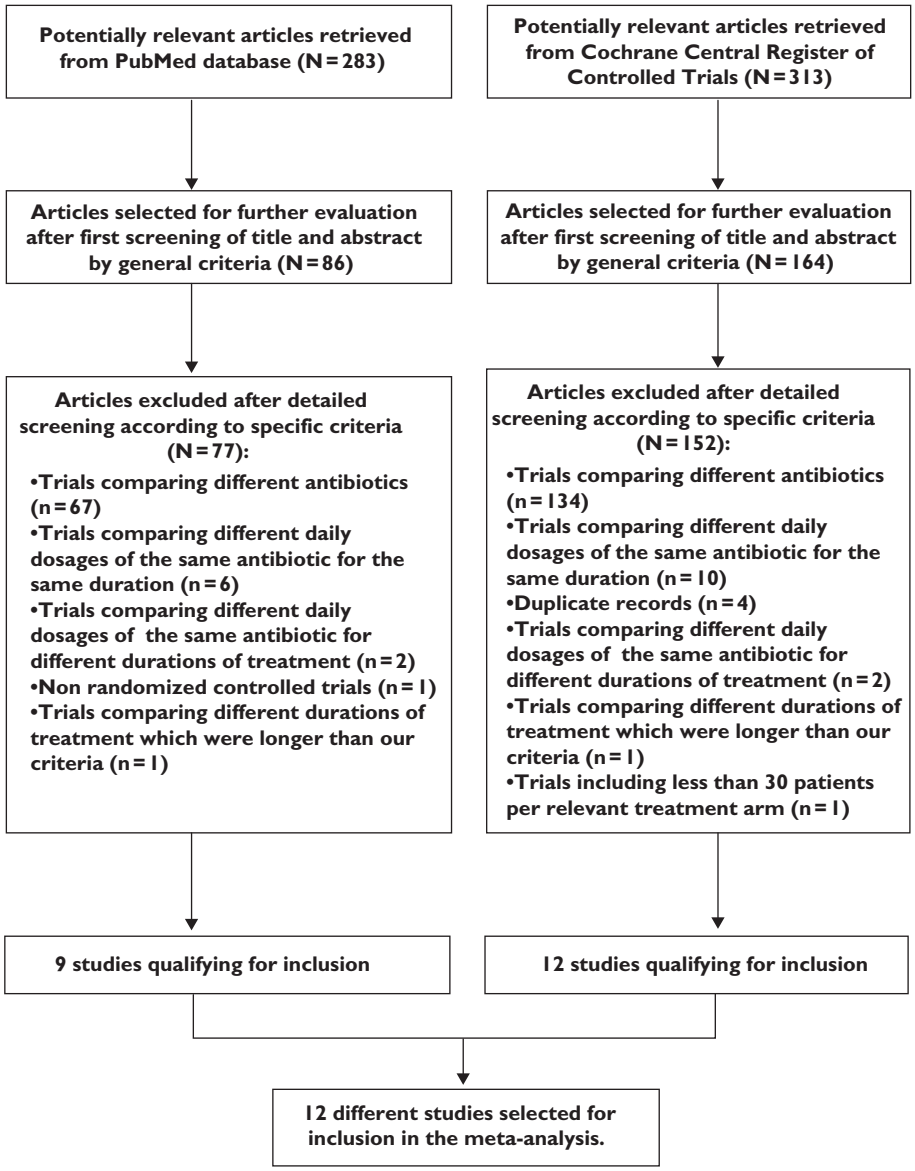

Figure 1

Flow diagram of the detailed process of selection of articles for our meta-analysis

In the subset analysis involving trials using β-lactam agents [18, 19, 24, 26–28] there was no difference in clinical success between the short-course and long-course regimens (six RCTs, 2649 patients, FEM, OR 0.95, 95% CI 0.76, 1.20).

Microbiological efficacy

Data regarding microbiological efficacy were provided in three of 12 included RCTs [21, 22, 26]. There was no difference in microbiological efficacy between the short-course and the long-course regimens for the treatment of ABS (511 bacterial isolates, FEM, OR 1.30, 95% CI 0.62, 2.74, Figure 3).

Relapses

Data about relapses were provided in five of 12 RCTs [18, 21, 25–27]. No difference was found between the short-course and long-course regimens for the treatment of ABS (1396 patients, FEM, OR 0.95, 95% CI 0.63, 1.42).

In the sensitivity analysis comparing antimicrobial treatment of duration of 5 *vs.* 10 days [18, 21, 26, 27], there was no difference in relapses between the short-course and long-course regimens (four RCTs, 1344 patients, FEM, OR 0.91, 95% CI 0.60, 1.37).

In the subset analysis involving trials using β-lactam agents [18, 26, 27], there was no difference in relapses between the short-course and long-course regimens (three RCTs, 1075 patients, FEM, OR 0.90, 95% CI 0.58, 1.39).

Table 1

Main characteristics of the randomized controlled trials included in the meta-analysis

Author (year)	Study design	Population (age group — setting — type of sinusitis — prior duration — diagnostic criteria)	Short-course regimen (type — dosage — duration)	Long-course regimen (type — dosage — duration)	Concomitant therapy	ITT population (short course–long course arm)	PP population (short course–long course arm)	Timing of test-of-cure visit	Jadad score
Upchurch *et al.* (2006) [24]	Multicentre double-blind RCT	Adults (≥18 years old), outpatients with maxillary ABS for 7–28 days clinically and radiologically confirmed	Faropenem medoxomil 300 mg q12 h for 7 days	Faropenem medoxomil 300 mg q12 h for 10 days	Oral or nasal decongestants without steroids, antihistamines	729 (366–363)	575 (295–280)	Study day 17–31	5
Gehanno *et al.* (2004) [19]	Multicentre double-blind RCT	Adults (18–70 years old), outpatients with maxillary ABS for >3 days clinically and radiologically confirmed	Cefotiam axetil 200 mg q12 h for 5 days	Cefotiam axetil 200 mg q12 h for 10 days	Paracetamol	1018 (508–510)	800 (398–402)	Study day 10	5
Henry *et al.* (2003) [20]	Multicentre double-blind RCT	Adults (≥18 years old), outpatients with maxillary ABS for 7–28 days clinically and radiologically confirmed	Azithromycin 500 mg qd for 3 days	Azithromycin 500 mg qd for 6 days	Not allowed	613 (312–311)	543 (272–271)	Study day 22–36	4
Luterman *et al.* (2003) [21]	Multicentre double-blind RCT	Adults (≥18 years old), outpatients with ABS for <28 days clinically and radiologically confirmed	Telithromycin 800 mg qd for 5 days	Telithromycin 800 mg qd for 10 days	Analgesics, anti-inflammatory agents, cough preparations	498 (244–254)	286 (146–140)	Study day 17–24	3
Ferguson *et al.* (2002) [17]	Multicentre double-blind RCT	Adults (≥18 years old), outpatients with ABS for 7–28 days clinically and radiologically confirmed	Gemifloxacin 320 mg qd for 5 days	Gemifloxacin 320 mg qd for 7 days	NR	421 (218–203)	356 (181–175)	Study day 18–25	4
Gehanno *et al.* (2002) [26]	Multicentre double-blind RCT	Adults (≥18 years old), outpatients with maxillary ABS for ≥10 days clinically and radiologically confirmed	Cefpodoxime proxetil 200 mg q12 h for 5 days	Cefpodoxime proxetil 200 mg q12 h for 10 days	Local vasoconstrictors for the first 4 days, paracetamol	486 (236–250)	409 (194–215)	Study day 12–15	4
Roos *et al.* (2002) [22]	Multicentre double-blind RCT	Adults (18–65 years old), outpatients with ABS for <28 days clinically, radiologically and microbiologically confirmed	Telithromycin 800 mg qd for 5 days	Telithromycin 800 mg qd for 10 days	Not allowed	335 (167–168)	256 (123–133)	Study day 17–21	3
Sher *et al.* (2002) [23]	Multicentre investigator-blinded RCT	Adults (≥18 years old), outpatients with maxillary ABS for ≥7 days clinically and radiologically confirmed	Gatifloxacin 400 mg qd for 5 days	Gatifloxacin 400 mg qd for 10 days	Decongestants, antihistamines	290 (149–141)	264 (137–127)	7–14 days after the completion of treatment	4
Dubreuil *et al.* (2001) [27]	Multicentre double-blind RCT	Adults (≥18 years old), outpatients with maxillary ABS clinically and radiologically confirmed	Cefuroxime axetil 250 mg q12 h for 5 days	Cefuroxime axetil 250 mg q12 h for 10 days	Paracetamol, fenoxazoline	401 (206–195)	354 (176–178)	Study day 10	5
Gehanno *et al.* (2000) [18]	Multicentre double-blind RCT	Adults (≥18 years old), outpatients with ABS for <10 days clinically and radiologically confirmed	Amoxicillin-clavulanate 500 mg q8 h for 5 days	Amoxicillin-clavulanate 500 mg q8 h for 10 days	Methylprednisolone 8 mg q8 h for 5 days after randomization	417 (205–212)	360 (181–179)	Study day 14	4
Pessey *et al.* (1996) [28]	Multicentre double-blind RCT	Adults (≥18 years old), outpatients with ABS (maxillary, frontal or ethmoid) for <5 days clinically and radiologically confirmed	Cefixime 200 mg q12 h for 4 days	Cefixime 200 mg q12 h for 10 days	Prednisolone 40 mg qd, oxymetazoline q8 h	165 (80–85)	165 (80–85)	Study day 11–15	4
Williams *et al.* (1995) [25]	RCT	Adults (≥18 years old), male outpatients with maxillary ABS clinically and radiologically confirmed	Trimethoprim/ sulfamethoxazole 160/800 mg q12 h for 3 days	Trimethoprim/ sulfamethoxazole 160/800 mg q12 h for 10 days	Oxymetazoline, other decongestants, antihistamines	80 (40–40)	76 (39–37)	Study day 14	5

ITT, intention-to-treat; NR, not reported; PP, per protocol; qd, every 24 h; q12 h, every 12 h; q8 h, every 8 h; RCT, randomized controlled trial.

Table 2

Data from the included randomized controlled trials regarding the primary and secondary outcomes of the meta-analysis

Author (year)	Clinical success, *n/N* (%)		Microbiological efficacy, *n/N* (%)		Relapses, *n/N* (%) (evaluation time, days)		Time to resolution of symptoms, mean ± SD		Patients with adverse events, *n/N* (%)		Patient withdrawals due to adverse events, *n/N* (%)	
	Short course	Long course	Short course	Long course	Short course	Long course	Short course	Long course	Short course	Long course	Short course	Long course
Upchurch *et al.* (2006) [24]	237/295 (80.3%)	229/280 (81.8%)	NR	NR	NR	NR	12.8 ± 4.8	12.7 ± 4.9	81/366 (22.1%)‡	73/363 (20.1%)‡	9/366 (2.5%)	13/363 (3.6%)
Gehanno *et al.* (2004) [19]	353/398 (88.7%)*	356/402 (88.6%)*	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Henry *et al.* (2003) [20]	195/272 (71.7%)*	199/271 (73.4%)*	NR	NR	NR	NR	NR	NR	97/312 (31.1%)	117/311 (37.6%)	7/312 (2.2)	11/311 (3.5%)
Luterman *et al.* (2003) [21]	110/146 (75.3%)	102/140 (72.9%)	6/7 (85.7%)§	6/7 (85.7%)§	5/136 (3.7%) (d31–45)	5/133 (3.8%) (d31–45)	NR	NR	103/244 (42.2%)‡	119/254 (46.6%)‡	16/244 (6.6%)‡	14/254 (5.5%)‡
Ferguson *et al.* (2002) [17]	158/181 (87.3%)	152/175 (86.9%)	NR	NR	NR	NR	NR	NR	73/218 (33.5%)	82/203 (40.4%)	2/218 (0.9%)	1/203 (0.5%)
Gehanno *et al.* (2002) [26]	185/194 (95.4%)	196/215 (91.2%)	84/88 (95.5%)§	90/99 (90.9%)§	7/194 (3.6%) (d12–15)	15/215 (7%) (d12–15)	NR	NR	24/236 (10.2%)‡	20/250 (8%)‡	6/236 (2.5%)	2/250 (0.8%)
Roos *et al.* (2002) [22]	112/123 (91.1%)	121/133 (91%)	78/86 (90.7%)§	84/92 (91.3%)§	NR	NR	NR	NR	50/166 (30.1%)	64/167 (38.3%)	6/166 (3.6%)	1/167 (0.6%)
Sher *et al.* (2002) [23]	102/137 (74.4%)	101/127 (79.5%)	NR	NR	NR	NR	NR	NR	NR	NR	2/149 (1.3%)‡	5/141 (3.5%)‡
Dubreuil *et al.* (2001) [27]	151/170 (88.8%)	150/170 (88.2%)	NR	NR	25/168 (14.9%) (d21–28)	26/161 (16.1%) (d21–28)	Up to 5 days	Up to 5 days	12/206 (5.8%)‡	23/195 (11.8%)‡	3/206 (1.5%)‡	7/295 (2.4%)‡
Gehanno *et al.* (2000) [18]	142/181 (78.5%)*	151/179 (84.4%)*	NR	NR	11/162 (6.8%) (d30)	7/175 (4%) (d30)	NR	NR	20/213 (9.4%)‡	26/220 (11.8%)‡	1/213 (0.5%)‡	7/220 (3.2%)‡
Pessey *et al.* (1996) [28]	70/80 (87.5%)*	77/85 (90.6%)*	NR	NR	NR	NR	5.7 ± 3.2	5.3 ± 2.9	12/82 (14.6%)‡	4/86 (4.7%)‡	0/82(0%)‡	0/86(0%)‡
Williams *et al.* (1995)[25]	30/39 (76.9%)	28/37 (75.7%)	NR	NR	3/27† (11.1%) (up to d30)	1/25† (4%) (up to d30)	RR¶ = 1.0, 95% CI 0.97, 1.04		14/40(35%)	10/40(25%)	0/40(0%)	0/40(0%)

*Only data on cure were reported. †One additional patient had recurrence between days 30–60. ‡Only adverse events deemed as drug-related were reported. §Data represent eradication plus presumed eradication of pretreatment isolated pathogens. ¶Risk ratio of longer symptom duration between the two groups. D, day(s); CI, confidence interval; NR, not reported.

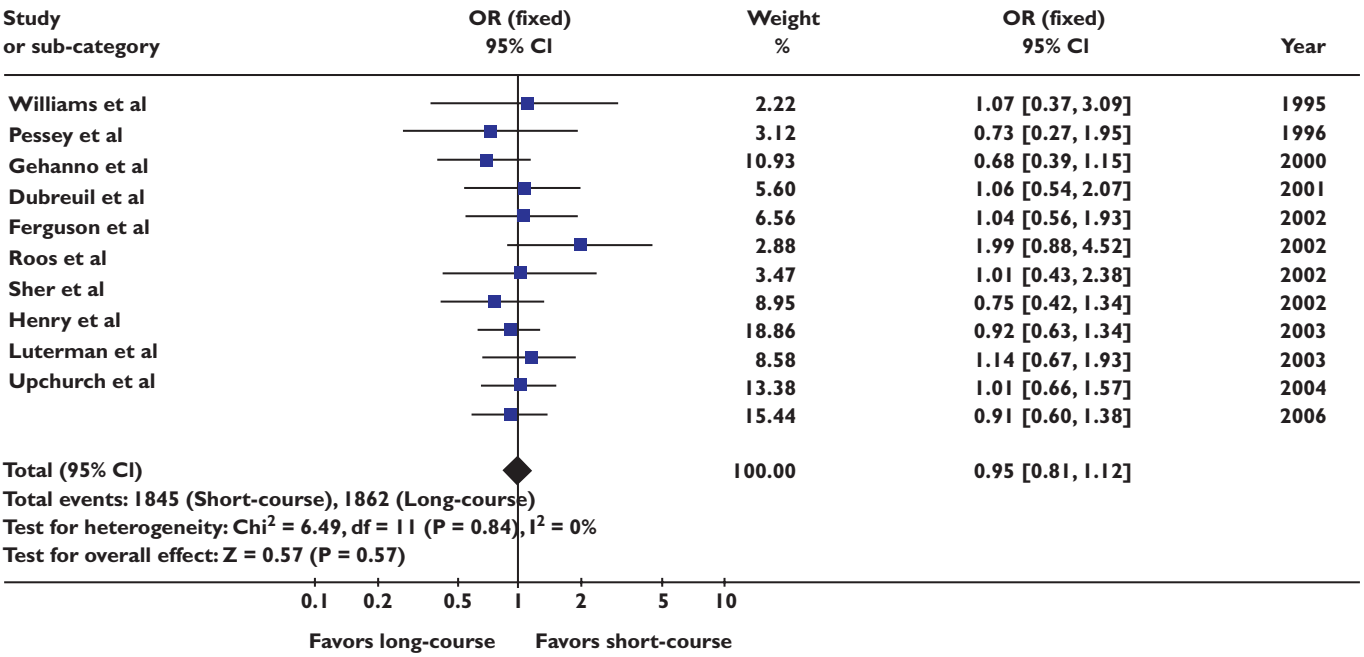

Figure 2

Meta-analysis of clinical success at the test-of-cure assessment of per protocol patients treated with short-course *vs.* long-course antibiotic regimens. (Vertical line: 'no difference' line between compared treatments; horizontal lines: 95% confidence intervals; squares: point-estimates; size of the squares: weight of the study in the meta-analysis; diamond shape: pooled odds ratio plus 95% confidence interval)

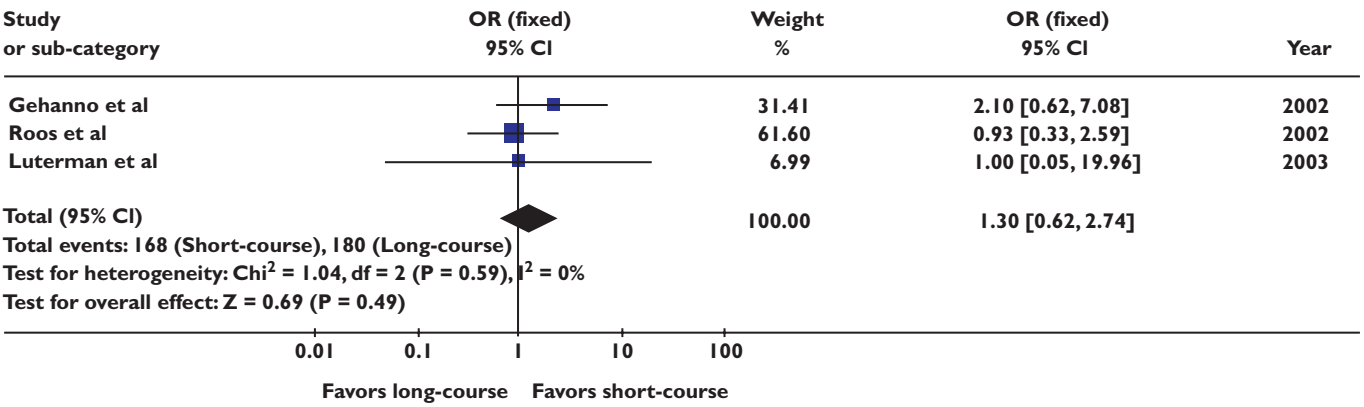

Figure 3

Meta-analysis of microbiological efficacy against pretreatment isolated pathogens treated with short-course *vs.* long-course antibiotic regimens. (Vertical line: 'no difference' line between compared treatments; horizontal lines: 95% confidence intervals; squares: point-estimates; size of the squares: weight of the study in the meta-analysis; diamond shape: pooled odds ratio plus 95% confidence interval)

Adverse events

Data about patients with adverse events were provided in 10 out of 12 RCTs [17, 18, 20–22, 24–28]. There was no difference in the percentage of patients with adverse events between the short-course and long-course regimens for the treatment of ABS (4172 patients, REM, OR 0.88, 95% CI 0.71, 1.09, Figure 4).

In the sensitivity analysis comparing antimicrobial treatment of duration of 5 *vs.* 10 days [18, 21, 22, 26, 27], fewer adverse events were observed in patients treated with short-course regimens compared with patients treated with long-course regimens (five RCTs, 2151 patients, FEM, OR 0.79, 95% CI 0.63, 0.98).

In the subset analysis involving trials using β-lactam agents [18, 24, 26–28], there was no difference in the percentage of patients with adverse events between the short-course and long-course regimens (five RCTs, 2217 patients, REM, OR 1.03, 95% CI 0.65, 1.62).

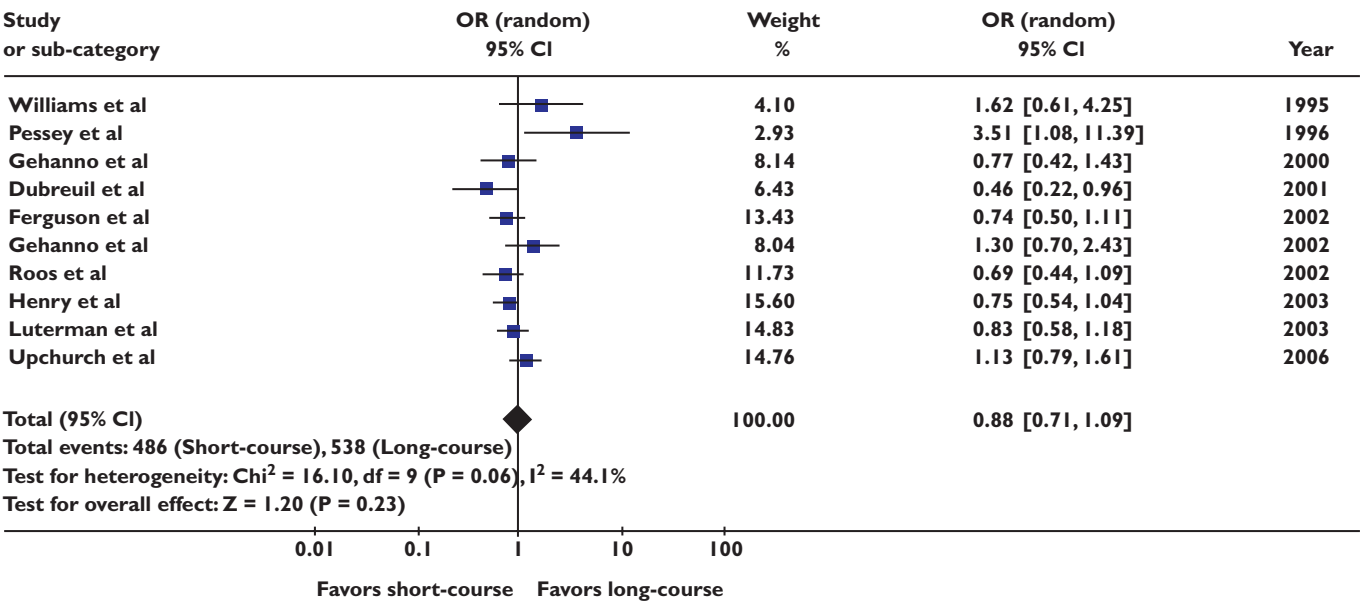

Figure 4

Meta-analysis of adverse events reported for patients treated with short-course *vs.* long-course antibiotic regimens. (Vertical line: 'no difference' line between compared treatments; horizontal lines: 95% confidence intervals; squares: point-estimates; size of the squares: weight of the study in the meta-analysis; diamond shape: pooled odds ratio plus 95% confidence interval)

Withdrawals due to adverse events Data about withdrawals of patients due to adverse events were provided in 11 out of 12 RCTs [17, 18, 20–28]. There was no difference in withdrawals due to adverse events between the short-course and long-course regimens for the treatment of ABS (4562 patients, FEM, OR 0.88, 95% CI 0.61, 1.29).

In the sensitivity analysis comparing antimicrobial treatment of duration of 5 *vs.* 10 days [18, 21–23, 26, 27], there was no difference in withdrawals due to adverse events between the short-course and long-course regimens (six RCTs, 2541 patients, FEM, OR 1.02, 95% CI 0.63, 1.64).

In the subset analysis involving trials using β-lactam agents [18, 24, 26–28], there was no difference in withdrawals due to adverse events between the short-course and long-course regimens (five RCTs, 2317 patients, FEM, OR 0.71, 95% CI 0.39, 1.27).

Discussion

The findings of this meta-analysis suggest that there is no difference in terms of effectiveness and safety between short-course and long-course antibiotic regimens for the treatment of uncomplicated ABS in adults. The findings of subset and sensitivity analyses were consistent, with the exception of the sensitivity analysis for patients with adverse events, which were fewer, albeit with marginal statistical significance, in patients that received a 5-day course of therapy compared with a 10-day regimen.

Longer duration of antibiotic treatment might have disadvantages, compared with equally effective shorter duration treatment, including higher toxicity, poorest patient compliance, promotion of bacterial drug resistance and greater overall economic burden. Regarding toxicity, the most common adverse events reported in the RCTs included in our meta-analysis were gastrointestinal in nature, consisting primarily of diarrhoea and nausea/vomiting. Although these are frequently nonsevere, they can cause considerable patient discomfort and decrease compliance with therapy.

Furthermore, increasing bacterial drug resistance is a major concern worldwide, and, apart from unwarranted antibiotic use, long exposure and interaction of bacteria with antimicrobial agents is considered to be one of the important contributing factors [29, 30]. Regarding the main causative pathogens of ABS, the rates of *S. pneumoniae* strains with reduced susceptibility to penicillin, and of β-lactamase-producing strains of *H. influenzae* and *M. catarrhalis* have considerably increased [31–34]. Notably, in children treated with a low-dose β-lactam agent for a prolonged period of time, a higher risk of carriage of penicillin-resistant *S. pneumoniae* in the nasopharynx has been noted [35]. Prolonged antimicrobial therapy is often associated with poor patient compliance after the resolution of symptoms or because of toxicity, a fact that may lead to inappropriately low drug levels, thus facilitating the emergence of resistance [36–39]. Last, but not least, the economic benefits of shortened, although equally effective, treatment should not be disregarded, since at

a community level the cost of even 2 extra days of therapy may be appreciable [40].

It should be mentioned that the findings of this meta-analysis regarding the similar clinical effectiveness of short- and long-duration treatment of ABS should not be interpreted without some further considerations. Respectively, as has been shown in acute otitis media [41], factors such as the expected inclusion of many patients with self-limiting viral disease [4], even with the use of imaging diagnostic criteria [42], along with the persistence of sinusitis-like symptoms regardless of potential bacterial eradication [4], and the administration of adjunctive symptom-relief medications [43], could potentially blunt differences between compared treatments in trials of ABS.

This is exemplified by the fact that the added clinical effectiveness of antibiotics *vs.* placebo in ABS, demonstrated in relevant RCTs, has been, at most, modest. In a recent meta-analysis of RCTs involving patients with clinically or radiographically diagnosed ABS, the margin of added clinical benefit conferred by antibiotics was found to be approximately 10% [44]. This relatively small margin of clinical benefit of antibiotics *vs.* placebo may leave little space for the demonstration of relevant differences between long- and short-course antibiotic regimens. However, the total sample size of the RCTs included in our meta-analysis could be considered as adequate for the demonstration of a small, clinically relevant decrease in the clinical success rate of short-course compared with long-course antibiotic treatment. Nevertheless, true differences between the compared treatments could be better manifested in studies employing microbiological diagnostic and assessment criteria [45]. Our meta-analysis did not show a difference between shorter and longer treatment of ABS, in terms of microbiological efficacy, although this was based on a small number of trials and on presumed rather than microbiologically documented eradication.

It should be emphasized that the value of routine administration of antibiotics in patients with symptoms and signs of acute sinusitis is disputed [46]. This is related to the fact that most patients with such manifestations are expected to have self-limiting disease of viral aetiology [46]. No unique relevant sign or symptom can accurately predict the need for the administration of antibiotics [47]. It largely relies on the clinician's own judgment, taking into consideration a constellation of clinical parameters, to single out those patients who are likely to have disease of bacterial aetiology, and thus be candidates for antibiotic therapy. However, data show that antibiotics are overused for the treatment of ABS in primary care services [46]. Our meta-analysis suggests that, if antibiotics are to be used, shorter course regimens may be as effective as traditional longer course ones for the vast majority of patients who have mild to moderate disease. Limiting the duration of antibiotic treatment may spare some of the untoward effects of antibiotic overuse, regarding both the patient and the community level.

Longer courses of antibiotics may still be necessary for the treatment of patients with other types of ABS, such as frontal or ethmoid, since they can lead to serious or even life-threatening complications, if treated unsuccessfully [48, 49]. Moreover, patients with complicating factors, such as immunosuppression or chronic underlying diseases, who have been excluded from the RCTs of this meta-analysis, should not be considered as candidates for a short course of therapy.

The main strength of our meta-analysis is that it is based on a sufficient number of mostly double-blind, high-quality RCTs, which employed similar and rigorous diagnostic inclusion criteria. Additionally, it excluded trials that compared between different antibiotic agents, with potentially diverse pharmacokinetics and consequently duration of action, a factor that could confound outcomes. The antibiotics used in the great majority of the included RCTs have a relatively short half-life, thus, short duration of administration translates to short course of treatment. The only exception is one RCT that evaluated treatment with azithromycin, which has a relatively extended half-life and can retain appreciable tissue levels long after the discontinuation of treatment [50].

In conclusion, the findings of this meta-analysis suggest that short-course antibiotic treatment (median 5 days) is as effective as longer-course treatment (median 10 days) for patients with acute uncomplicated bacterial sinusitis. Considering that traditional 10-day regimens may be associated with greater toxicity and impose a greater risk for the development of bacterial drug resistance and a greater economic burden as well, shorter duration regimens may become the standard of ABS treatment. Even so, we would underscore the importance of the clinician's own assessment, so that antimicrobial therapy should not inappropriately be curtailed in a patient not adequately responding to the regimen administered.

Competing interests

None to declare.

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